Modeling of the human circadian clock: *per3* provides molecular support for behavioral observations

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The human circadian clock controls daily patterns of sleep-wake and activity cycles. Circadian clock malfunctions can lead to serious pathologies, ranging from obesity and diabetes to cancer. The human circadian clock consists of a core negative feedback loop: *period* genes (*per1-3*) and *cryptochromes1-2* (*cry1-2*) are activated by the BMAL1-CLK protein complexes; the translated PER and CRY proteins in turn inhibit the transcription of BMAL1-CLK. The *per3* gene is often believed to be unimportant to this network, since the biological clock continues to function in the absence of *per3*. However, recent research has causally linked *per3* to numerous sleep disorders and behavioral conditions. Here, we developed for the first time a comprehensive mathematical model of the human circadian clock consisting of nine genes, including *per3*. We performed parameter searches to demonstrate that our model can reproduce the dynamics of the human circadian clock in more than ten mutant conditions. Using our model we also predicted the circadian clock dynamics in four recently discovered *per3* mutant genetic backgrounds that have been linked to human sleep and behavioral disorders. Our results support the current experimental observations that shows *per3* gene is important for the correct functioning of the circadian clock, and suggests that further research has to be done on *per3* gene for true understanding of human circadian clock.